REMARKS/ARGUMENTS

Claims 1-69 were examined in the above-identified application. Claims 17-20, 24, 38-41, and 45-69 have been withdrawn by the Examiner as being directed to a non-elected invention. Claims 2, 15 -24 and 36-69 have been canceled without prejudice to Applicants' right to prosecute the subject matter encompassed by the claims in a related, co-pending application. Claims 1, 4, 6, 7, 12, 25, 27, 28 and 33 have been amended. Support for these amendments is identified in the following remarks. No new matter is added by these amendments.

The Examiner has acknowledged Applicants' election with traverse of Group I (claims 1-16, 21, 23, 25-37, 42 and 44) filed on March 6, 2007. The requirement has been deemed proper and has been made FINAL. Claims 17-20, 24, 38-41 and 45-69 have been withdrawn by the Examiner from prosecution as being directed to a non-elected invention. By this amendment Applicants have cancelled claim 17-20, 24, 38-41 and 45-69, but request reconsideration of composition claims 46-69 subsequent to amendment to correspond with the compositions used in the method claims 1, 3-14. and 25-34 once the claims have been allowed.

Specification

The Examiner has objected to the title of the invention as not being descriptive. A new title has been required that would be clearly indicative of the invention to which the claims are directed. Applicants have amended the title of the invention to recite "Methods for inducing an antigen specific systemic and rectal cytotoxic T cell response by contacting antigen with the rectal mucosal tissue of a subject."

The Examiner has also required Applicants to update the first paragraph of the specification to provide the correct status of each application. Applicants have reviewed the status of each application and amended the first paragraph of the specification as required to update the status of all related applications.

Claim Objections

Claims 4, 7, and 12 are objected to by the Examiner because the Examiner has alleged that Claims 4, 7, and 12 recite improper Markush language (*i.e.*, "or" instead of "and"). Applicants do not believe that the language used in claims 4, 7 and 12 is improper, but in order to further expedite prosecution of the application claims 4, 7, 12 and 33 have been amended to recite "the cytokine is granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), interleukin-7 (IL-7), interleukin-12 (IL-12) or tumor necrosis factor α (TNF α)." The amendment of the claims is believed to obviate the rejection of the Examiner.

Rejections Under 35 U.S.C. §112

Claims 1-16, 21, 23, 25-37, 42 and 44 stand rejected under 35 U.S.C. §112, first paragraph, the Examiner believing that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In particular, the Examiner has alleged in an analysis of the specification and claims under the "Wands" factors that the instant invention is drawn to a method for inducing a protective rectal mucosal cytotoxic T lymphocyte (CTL) response in a mammalian subject comprising contacting a rectal mucosal tissue of the subject with a composition comprising any purified soluble antigen, including HIV and that the phrase "inducing a protective rectal mucosal CTL response" has been interpreted as indicating a vaccine. The Examiner has further concluded that the term "vaccine," by definition, implies a preparation intended for active immunological prophylaxis. Still further, the Examiner has asserted that prophylaxis is defined as the prevention of disease or of a process that can lead to disease.

The Examiner also believes that it is well known in the art and even to the general public that medical science, despite decades of intense research, has not found any antigen, immunogen, or compound that can be credibly used as a vaccine against HIV. A list of alleged

obstacles to developing a successful HIV vaccine are outlined by the Examiner. It is asserted by the Examiner that the existence of these obstacles prevents one of ordinary skill in the art from accepting any therapeutic regimen on its face given the intense interest in developing HIV treatments or vaccines and the lack of success in doing so.

The specification has been summarized by the Examiner as containing examples showing the vaccination of mice and the induction of antigen-specific CTLs. None of the examples are believed by the Examiner to show rectal mucosal vaccination and challenge with HIV resulting in complete protection or prevention of HIV infection. As the Examiner has concluded that the claimed invention is directed to a rectal mucosal vaccine against HIV, the Examiner believes that there is insufficient disclosure to reasonably predict that the claimed vaccine of the instant specification would prevent HIV infection. In addition, the Examiner has asserted that the disclosure fails to provide any guidance pertaining to the correlates of human protection. The Examiner further believes that the disclosure fails to provide any guidance pertaining to the development of a persistent and protective HIV-1-specific immune response. It is also alleged by the Examiner that Applicants have not provided any evidence in the instant specification that the disclosed immunogens can prevent HIV infection or HIV-1 transmission following the administration of said vaccine. The Examiner has alleged that the state-of-the-art vis-à-vis HIV vaccine development is one of unpredictability and that to date, there is not one single effective HIV vaccine on the market and that it would require undue experimentation for one skilled in the art to practice the claimed invention.

Although Applicants disagree with all of the above assertions and inferences made by the Examiner, claims 1 and 25 have been amended to recite "[a] method for inducing an antigen specific systemic and rectal mucosal cytotoxic T lymphocyte (CTL) response in a mammalian subject comprising contacting a rectal mucosal tissue of the subject with a composition comprising a chimeric peptide having the amino acid sequence KQIINMWQEVGKAMYAPPIS GQIRRIHIGPGRAFYTTKN (SEQ ID NO:9)." Applicants believe that each of the reasons raised by the Examiner in support of the rejection under 35 U.S.C. § 112, first paragraph, are not relevant to the invention as now claimed. The specification

as filed demonstrates that the chimeric peptide of claim 1 can induce a systemic and rectal mucosal antigen specific cytotoxic T cell response. As such, a showing, for example, of protection from HIV of any isolate is not required, nor is evidence that the methods of the present invention to induce an HIV-1-specific immune response specific to any HIV isolate or evidence that the disclosed peptide can prevent HIV infection or HIV transmission necessary for written description of the invention as now claimed.

The Examiner has noted that claims 6 and 27 recite the limitation "the cytokine" in reference to claims 1 and 25, respectively. It is the opinion of the Examiner that there is insufficient antecedent basis for this limitation in the claims. Applicants have reviewed the claims and although Applicants believe the limitation to have proper antecedent basis, claims 6 and 27 have been amended to depend upon claims 5 and 26, respectively. The amendment is believed to further provide proper basis for the phrase "the cytokine".

Rejections Under 35 U.S.C. §102

Claims 1-4 and 15 stand rejected under 35 U.S.C. §102(a) as being anticipated by Klavinskis *et al.* (*J. Immunol.*, 1996, 157:2521-2527). Klavinskis *et al.* is alleged by the Examiner to teach rectal and vaginal immunization by administering an SIV peptide covalently linked to cholera toxin B subunit (CTB) as an essential adjuvant. Klavinskis *et al.* is also alleged by the Examiner to show that CTLs were isolated from the rectal mucosa and antigen-specific (see page 2524).

Applicants traverse the rejection of claims 1-4 and 15 as anticipated by Klavinskis *et al.* Further, Applicants have amended claim 1 to provide greater clarity and particularity to the invention claimed. In particular, claim 1 has been amended to recite "[a] method for inducing an antigen specific systemic and rectal mucosal cytotoxic T lymphocyte (CTL) response in a mammalian subject comprising contacting a rectal mucosal tissue of the subject with a composition comprising a chimeric peptide having the amino acid sequence KQIINMWQEVGKAMYAPPIS GQIRRIHIGPGRAFYTTKN (SEQ ID NO:9)."

Klavinskis *et al.* do not disclose the claimed invention. In particular, Klavinskis *et al.* disclose the administration of a virus-like particle comprising an SIV gag peptide to lymph nodes and to the rectal mucosa of a mammalian subject. The composition also must comprise an adjuvant to induce the immune response. Claim 1 as amended is directed to a method for inducing a systemic and rectal mucosal antigen specific cytotoxic T cell response using a chimeric peptide having particular defined amino acid sequences from the HIV envelope region. As such the disclosure of a viral-like particle having an unrelated SIV gag peptide can not anticipate the claimed invention.

Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-4 and 15 under 35 U.S.C. § 102(a) as being anticipated by Klavinskis *et al.* (*J. Immunol.*, 1996, 157:2521-2527) in view of the amendment of claim 1 and the remarks above.

Rejections Under 35 U.S.C. §103

Claims 5-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Klavinskis *et al.* in view of Kiyono *et al.* (*Adv. Drug Delivery Rev.*, 18:23-51, 1995) and Ahlers *et al.* (*J. Immunol.*, 158:3947-3958, 1997). The Examiner has summarized the claims of the present invention as being drawn to a method for inducing a protective rectal mucosal cytotoxic T lymphocyte (CTL) response in a mammalian subject comprising contacting a rectal mucosal tissue of the subject with a composition comprising "a purified soluble antigen, wherein the method further comprises administering a purified cytokine, *e.g.*, GM-CSF. IL-2, IL-7, IL-12, IFN-γ or TNF-α, to the subject.

The teachings of Klavinskis *et al.* as alleged by the Examiner are outlined above. Further, the Examiner has noted that Klavinskis *et al.* does not teach administering a cytokine to the subject. However, the Examiner alleges that Ahlers *et al.* teaches immunizing a subject with the peptide of SEQ ID NO:9 and various cytokines (GM-CSF, IL-2, IL-12, IFN-γ or TNF-α) and that Ahlers *et al.* found that GM-CSF synergized with IL-12 for CTL induction. Ahlers *et al.* is

also alleged to show that TNF-α synergized with IL-12, but by a different mechanism, inducing IFN-γ production, thus shifting the response to a Th1 phenotype (see abstract). The Examiner also believes that Ahlers *et al.* suggest that in addition to IL-2, optimum induction of $CD8^+$ *in vivo* requires a combination of cytokines, including GM-CSF and IL-12 (steering the Th response toward Th1 cytokines). As such, the Examiner concludes that it would have been obvious to one of ordinary skill in the art to modify the method taught by Klavinskis *et al.* to also administer cytokines to the subject.

It is further alleged by the Examiner that one would have been motivated to combine the references given the suggestion by Kiyono *et al.* that the cell-derived cytokines are essential for the induction of appropriate antigen-specific mucosal immune responses (see bottom of page 23) and the teachings of Ahlers *et al.* The Examiner believes that there would have been a reasonable expectation of success given the findings of Ahlers *et al.* with regard to CTL induction by cytokines. Thus, the Examiner concludes that the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicants strongly disagree with the comments and conclusions of the Examiner. As above, the primary reference, Klavinskis *et al.*, does not teach or suggest the peptide compositions of the present invention. Further, any combination with Klavinskis *et al.* would merely suggest combining a virus-like construct with a cytokine or a prior disclosed peptide. None of these suggestions provide any basis for leading to the present invention as claimed. As such, Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 5-14 under 35 U.S.C. § 103(a) as being unpatentable over Klavinskis *et al.* in view of Kiyono *et al.* (*Adv. Drug Delivery Rev.*, 18:23-51, 1995) and Ahlers *et al.* (*J. Immunol.*, 158:3947-3958, 1997).

Claims 16, 21, and 23 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Klavinskis *et al.*, above, and either Ahlers *et al.*, above, or Berzofsky *et al.* (WO 94/26785). The alleged teachings of Klavinskis *et al.* are outlined above and although the Examiner does not believe that Klavinskis *et al.* teach SEQ ID NO:9 or an antigen from HIV-1,

the Examiner alleges that both Ahlers *et al.* and Berzofsky *et al.* disclose the peptide of SEQ ID NO:9 (see page 3948 of Ahlers *et al.* and SEQ ID NO:28 and claim 15 of Berzofsky *et al.*). Both references are summarized by the Examiner as describing the peptide of SEQ ID NO:9 as being derived from HIV-1, as an inducer of cytotoxic T cells, and useful for therapeutic or prophylactic vaccines against HIV. As such, the Examiner believes that it would have been obvious to one of ordinary skill in the art to modify the method taught by Klavinskis *et al.* to administer the peptide of SEQ ID NO:9 as a vaccine to a subject. Motivation to combine the references, the Examiner alleges, is an alleged suggestion in Klavinskis *et al.* that to prevent dissemination of HIV to the regional lymph nodes, an effective vaccine may need to stimulate CTL in the rectal or genital tract, and the teachings of Ahlers *et al.* and Berzofsky *et al.* that SEQ ID No:9 contains an immunodominant HIV CTL epitope. The Examiner believes that there would have been a reasonable expectation of success given the findings of Klavinskis *et al.* that mucosal or targeted lymph node immunization generates antigen-specific CTL in the rectal and genital mucosa. As such, the Examiner asserts that the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicants must again respectfully disagree with the reasoning and conclusions of the Examiner. In particular, as set forth above, Klavinskis *et al.* teach immunization of a subject with a virus-like particle that comprises the SIV p27 gag gene. The construct of Klavinskis *et al.* presents the antigen as a particulate antigen which is processed by the immune system differently than a soluble antigen, such as a polypeptide. As such, any combination with Ahlers *et al.* and/or Berzofsky *et al.* would not disclose or suggest the present invention. At most, there is a suggestion of incorporating the amino acid sequence of SEQ ID NO: 9 into the virus-like construct of Klavinskis *et al.* and administering the construct to a patient. Making and administering such a construct does not disclose or suggest the methods of the present invention.

The Examiner is respectfully requested to reconsider and withdraw the rejection of claims 16, 21, and 23 under 35 U.S.C. §103(a) as being unpatentable over Klavinskis *et al.*, above, and either Ahlers *et al.*, above, or Berzofsky *et al.* (WO 94/26785) in view of the above amendments and remarks.

Double Patenting

Claims 1-16 and 25-37 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-40 of U.S. Patent No. 6,749,856 (the '856 patent). The Examiner believes that although the conflicting claims are not identical, they are not patentably distinct from each other because there is overlapping subject matter between the groups of claims. Specifically, the Examiner alleges that the scope of the instant claims encompasses the scope of the '856 patent claims.

Applicants have amended claim 1 to recite "[a] method for inducing an antigen specific systemic and rectal mucosal cytotoxic T lymphocyte (CTL) response in a mammalian subject comprising contacting a rectal mucosal tissue of the subject with a composition comprising a chimeric peptide having the amino acid sequence KQIINMWQEVGKAMYAPPIS GQIRRIHIGPGRAFYTTKN (SEQ ID NO:9)" in order to point out the claimed invention with greater particularity and to comply with the restriction requirement that has been made final by the Examiner. Although Applicant does not agree that restriction of the present invention should have been made as directed by the Examiner, such amendment limits the present invention to a single polypeptide, that having the amino acid sequence as depicted as SEQ ID NO:9. There is no overlapping subject matter between the pending claims of the present application and U.S. Patent 6,749,856. Withdrawal of the present rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 2 October 2007

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